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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/767,041	01/22/2001	Hilda E. Smith	4726US	3344

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EXAMINER	
DUFFY, PATRICIA ANN	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 09/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/767,041	SMITH, HILDA E.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15,18,21-25,32,33,35-40 and 50-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15,18,21-25,32,33,35-40 and 50-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *see attached*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date: _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO AMENDMENT

The amendment filed 6-22-04 has been entered into the record. Claims 15, 18, 21-25, 32, 33, 35-40, 50-57 are pending and under examination.

The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

The following documents have not been received by the Patent Office at this time. 1- certified copy of EP 98202456.5; 2- New Oath/Declaration; and 3- English translation of the Abstract of EP 0750043A1.

The examiner acknowledges the filing of the certified copy of EP98202467.1. An initialled copy of the Information Disclosure statement filed 6-22-04 is enclosed with the exception of EP 0750 043 A1, that still is not in compliance with 37 CFR 1.198.

Rejections Withdrawn

The rejection of claims 16, 17, 31 and 34 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is moot in view of the cancellation of the claims.

The rejection of claims 16, 17, 31 and 34 are rejected 35 U.S.C. 102(b) as being clearly anticipated by Yother et al (WO 95/31548, published 23 November 1995, of record on 1449) is moot in view of the cancellation of the claims.

The rejection of the claims under 35 U.S.C. 102(a) as being clearly anticipated by Smith et al (Infection and Immunity, 67(4):1750-1756, April 1999, of record on 1449) is withdrawn in view of the filing of the priority document that teaches the relied upon gene-specific knockouts.

Rejections Maintained

Claims 52-55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained for reasons made of record for claims 15-25 and 31-51 in the Office Action mailed 1-20-04.

Applicant's arguments have been considered but are not persuasive. Applicants argue that the deficiency of capsular expression is the common structure or function. This is not persuasive, the issue is the lack of positively recited structure with respect to the capsular gene cluster and mutations thereof. The phenotype is a deficient capsule, this does not provide structure for a gene cluster. Genes are de facto described by nucleic acids and Applicants have not provided any structure of any gene cluster in the claims such the mutations can be envisioned. The specification at best provides two mutations in a particular gene cluster having a particular sequence. The specification does not describe other capsular gene clusters or the genus of mutations thereof. Mutations of genes are necessarily described by their corresponding nucleic acid sequences and Applicants have no structure in the claims and the specification does not teach the genus of mutations in an undefined gene structure. Applicants have not shown that they were in possession of the genus of *S. suis* gene mutants deficient in capsular expression as claimed because they have not described the genus of genes, nor the genus of mutants there of.

The rejection is maintained.

Claims 15, 18, 21-25, 32, 33, 35-40, 50-57 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained for reasons made of record for claims 15-25 and 31-51 in the Office Action Mailed 1-20-04.

Applicant's arguments have been carefully considered but are not persuasive. Applicants argue that "As long as the specification discloses at least one methods for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claims then the enablement is satisfied and cites In re Fischer, 427, F2d.833, 839, 166 USPQ 18, 24 (CCPA). In contrast to Applicants assertion the specification has not enabled how to make and use even one embodiment of the claimed invention. The specification teaches that the claimed mutants are useful for vaccines. The specification does not enable vaccines. The specification does not teach how to make a representative number of mutants that are in the scope of the now claimed invention. In contrast to Applicants assertion, there is no specific working example of any claimed mutant was tested as a vaccine therapeutic. Applicants argue that the capsular deficiency circumvent the difficulties related to heterologous protection since they do not rely on capsules to provide protection. This is not persuasive, there is no showing of protection against either the homologous strain or heterologous strains of *S. suis*. No protection data is provided in the specification as filed. Applicants' statement is a mere proposal lacking evidentiary support in the specification as filed. Applicants' assertions in the specification lack evidentiary support and are prophetic. The specification teaches that the vaccine strain of the invention is well suited to generate specific and long lasting immunity. There is not a single point of data regarding specific immune response, heterogeneous immune response or the degree of long lasting

immunity or protection from infection. The examiner has appropriately cited evidence that is reason to doubt the objective truth of the statements contained in applicants' specification. (*In re Marzocchi and Horton*, 169 USPQ 367 (CCPA 1971)). Applicants submit that the definition provided by the examiner is too limiting and that the description of the vaccine is more in line with the definition of a vaccine with respect to Merriam-Webster's On line dictionary. This is not persuasive, one skilled in this are would immediately envision protection needs to be demonstrated by a claimed vaccine, not mere immunogenicity. As provided by the examiner immunogenicity does not correlate with protection from infection. Further, the specification does not define a vaccine according to the recited dictionary. Vaccine and vaccination are medical and immunological terms and in the medical and immunological dictionaries, protection from infection is required. Applicants broad definition is not supported by the dictionaries of the art of which the invention is a part of, and is not supported by the specification as filed. Further, protection is conveyed at page 16 in the specification by means of controlling or eradicating disease. The specification specifically recites at page 14 "With a vaccine, as provided by the invention, that is derived from a specific Streptococcus mutant that is deficient in capsular expression, the difficulties relating to lack of heterologous protection can be circumvented since these mutants do not rely on capsular antigens, per se, to induce protection." Clearly, at the time of filing the specification correlates the term vaccine with protection and not broadly with immune response. As clearly, the art at the time of filing indicates that the capability to generate an immune response is not correlated with protection from disease. Applicants submit later studies published well after the filing date to demonstrate that the vaccine is protective. This is not persuasive, enablement must be established at the time of filing not at some later date. The courts have held that the specification must have been enabling at the time the

invention was made and developments after the time of filing are of no consequence to what one skilled in the art would have believed at the time of filing (*In re Wright*, 27 USPQ2d 1510). It is noted that enablement must be established in the specification at the time of filing and is to be commensurate in scope with the stated claimed see *In re Hogan and Banks*, 194 USPQ 527 (1977) and the courts have held that the disclosure is insufficient when testing is necessary to determine the actual use or possible lack of use *(In re Kirk and Petrow* (CCPA) 153 USPQ 48). In the instant case, one skilled would have to test to see if even one embodiment worked and as such, the specification is not enabled. Applicants point to pages 28 and 39 of the specification that discloses a challenge experiment. The examiner has carefully examined pages 28 and 39 of the current specification and neither page discloses challenge experiments using any of the described mutants. It appears that applicants reference page 25 of the substitute specification paragraph [00128]. This passage is appears prophetic, it does not describe any results of any challenge experiments. Where are the results of this alleged experiment ? This alleged experiment is not described or disclosed in the results section. The testing for virulence of the specific acapsular mutants in germ-free piglets as set forth on page 35 [00161] is not a challenge experiment, no immunological markers were tested an the vaccine efficacy is not demonstrated nor tested according to the asserted parameters of page 25. Virulence does not correlate with results of experimental animals (see Gottschalk et al Journal of Clinical microbiology 37(12):424, December 1999 of record) and as such virulence cannot be used to reach definitive conclusions regarding the vaccine properties of any *S. suis* mutant. Further, no evidence of antibody production is taught by this specification at all, nor are any of the recited indicia of the alleged reported challenge experiment on page 25 [00128]. No art accepted indicia of specific or cross-reactive antibodies are shown in any animal model that is correlative with

protection from infection. As such, this specification is not enabled for the claimed invention because it discloses a single use for the claimed mutant, as a vaccine, and the use as a vaccine is not enabled by this specification as filed. Additionally, there is no evidence of record for protection using the *S. suis* mutant to express a non-streptococcus virulence protein or a *Streptococcus* virulence factor or antigenic determinant. The effects of using the claimed *S. suis* mutant as a vector for delivery of heterologous antigens and protection from disease using the presented heterologous antigens are not addressed in Applicants response.

The rejection is maintained for reason made of record.

Claims 15, 18, 21, 22, 23, 32, 33, 35, 36, 37, 38, 39, 52, 54 and 56 stand rejected under 35 U.S.C. 102(b) as being clearly anticipated by Charland et al (Microbiology, 144:325-332, February 1998, of record on 1449) is maintained for reasons made of record in the Office Action mailed 1-20-04.

Applicants argue that the reference is not a 102(b). With respect to the 102(b) aspect, Applicants do not receive priority for a foreign application more than one year from the date of the foreign application. The 102(b) date of this application is 1 year back from the filing date of the international application to which Applicants claim priority. Anything published one year back from the international filing date is considered 102 (a) references here. Since the 1 year time point is reached on July 19, 1999 any publication with a date before July 19, 1998 is in fact prior art under 102(b). Charland et al was published February 1998 and is properly applied under 35 USC § 102(b). Applicants argue that the transconjugants are not stable and cite page 326. There exists no apparent teaching on page 326 that the mutants were not stable. This is also not persuasive, the transconjugants of Charland et al are produced recombinantly. The specification teaches that "Recombinant techniques useful in producing such

mutants are, for example, homologous recombination, transposons mutagenesis and other, wherein deletions, insertions or point(mutation) are introduced into the genome. Advantages of using recombinant techniques include the stability of the obtained mutants (especially with homologous recombination and double cross-over techniques), and the knowledge about the exact site of the deletion, mutation or insertion". (see marked up specification [0047-0048]). Given this teaching because a recombinant technique was used, the mutation is stable. Stable is not further defined in the specification and is not defined nor delimited in the specification to include only specific type of recombinant techniques nor type of mutation. Since the mutants of the art are produced recombinantly by conjugative transposon mutagenesis a process that by definition requires recombination. In view of the above, the rejection is maintained for reasons made of record for the above-recited claims.

New Rejections Based on Amendment

Applicant is advised that should claims 21-23, and 39 be found allowable, claims 35-37 and 39 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claims 15, 18, 21-25, 32, 33, 35-40, 50-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As to claims 15, 18, 21-25, 32, 33, 35-40, 50-57, the claims recite the term "stable". The term "stable" is not defined in the specification. The sole reference

to "stability" in the specification at paragraphs [0047-0048] of the marked up specification submitted on 6-22-04 that "Recombinant techniques useful in producing such mutants are, for example, homologous recombination, transposon mutagenesis and others, wherein deletions, insertions or point(mutations) are introduced into the genome. Advantages of using recombinant techniques include the stability of the obtained mutants (especially with homologous recombination and double cross-over techniques), and the knowledge about the exact site of the deletion, mutation or insertion". This passage does not teach the metes and bounds of the term stable and how it is assessed in regard to any particular mutation.

As to claim 35, this claim depends from claim 21 that recites the identical functional limitation and is not further limiting. As a result, claim 36 is identical to clam 22, claim 37 is identical to claim 23, claim 39 is identical to claim 40 and so on. The recitation of duplicative material is confusing and it is unclear what Applicants intend with these duplicative claims. Applicants should clarify for the record what the differences in scope are between these claims.

Claims 15, 18, 21-25, 32, 33, 35-40, 50, 51, 56 and 57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are drawn to a recombinant *Streptococcus sius* mutant deficient in capsular expression, wherein a mutation causing the deficiency in capsular expression is stable. The teachings of the specification are limited to two specific deletion mutations wherein a part of the *cps2B* gene of was replaced by the spectinomycin-resistance gene (mutant 10cpsB) and the 3' end of the *cps2E* gene as

well as the 5' end of the *cps2F* gene were placed by the spectinomycin-resistance gene (mutant 10cpsEF; see marked up specification [00159]). The deletions were made using nucleic acid sequence data obtained from the cloning of the particular genes. The teachings of the specification are limited to disruption of these two specific genes in *S. suis* provides for a phenotype of a mutant with deficient capsular expression. The current claims encompass any mutation anywhere in the entire *S. suis* genome that provides for a mutant with a phenotype with deficient capsular expression. The terms "recombinant" and "mutant" are seen to encompass insertions, deletions, point mutations, and inversions of particular sequences (see marked up specification [0047-0048]) that are "stable". The specification does not disclose any mutation outside of the particularly disclosed genes *cps2B* , *cps2E, cps2F* , that when disrupted provide for a mutant with a phenotype of deficient capsular expression. The disruption of 3 particular genes having particular sequences within an entire genome having a multitude of undisclosed and undescribed genes that may or may not impact capsular expression does not provide adequate written description support for the genus now claimed. Applicants own specification teaches that S. suis has at least 35 different serotypes and is remarkable heterogeneous. The specification teaches that many of the cloned serotype 2 genes are not conserved in the other 34 species of *S. suis* (see Table 4, page 134 of marked up specification). Similar findings were presented for serotypes 1 and 9 (Table 5, pages 135-136). Therefore, the teachings of the two serotype 2 deletion mutants using specific nucleotide sequences of specific genes does not provide description of the genus which is highly variant and includes loci outside of the particularly cps cloned genes described in the specification. The specification lacks written description of mutants and gene loci from a representative number of serotypes of *S. suis* that when mutated provide for the requisite deficient capsular expression. The claims specifically encompass

mutations by homologous recombination in loci outside of the particularly cloned cps loci. The specification fails to describe a single loci outside of the particularly cloned cps loci that would necessarily produce mutants as claimed. There is no characterization of such mutants and the specification describes none. The specification does not place any structure or chemical limitations on the mutants. The recitation of mutant deficient in capsular expression does not convey a common structure or function because the term deficient is described in the specification at [0045] and it is clear from this description that the term "deficient" does not provide similar structure or function. The term deficient includes no capsule, organization of the capsular material has been rearranged and others that have a nearly fully developed capsule that is only deficient in a particular sugar component. As such, the term deficient as it is recited in the claim does not and cannot provide a common structural or functional feature. The scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members are permitted. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description, because specific, not general guidance is needed. Since the disclosure fails to describe the common attributes or structural characteristics that identify members of the genus and because the genus is highly variant, the terms "mutant" and "deficiency in capsular expression" alone is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure of a two specific gene deletions in a single serotype of *S. suis*, fails to provide a representative number of species describe the claimed genus when the single function genus is highly diverse. Applicants were not in possession of the claimed genus because the specification does not convey to one of skill in the art a representative number of variants in structure and function of any such mutants

that have the claimed function of deficiency in capsular expression. The genus of polypeptides with the claimed function is substantial and highly variant because the polypeptides do not have a common structure and function. As such the specification lacks written description for the highly variant genus of single function mutants and one skilled in the art would not recognize that applicants had possession of the genus of claimed genus of *S. suis* mutants as instantly claimed.

Status of Claims

All claims stand rejected.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can generally be reached on M-F 6:30 am - 3:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864.

The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Pat a. Duffy

Patricia A. Duffy

Primary Examiner

Art Unit 1645